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Myasthenic syndromes

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ABSTRACT The neuromuscular junction is vulnerable to autoimmune attack both at the pre-synaptic nerve terminal and at the post-synaptic muscle membrane. Antibodies directed to the nicotinic acetylcholine receptor at the muscle surface are the cause of myasthenia gravis in the majority of cases. Myasthenia gravis is an acquired condition, characterised by weakness and fatigability of the skeletal muscles. The ocular muscles are commonly affected first, but the disease often generalises. Treatment includes symptom control and immunosuppression. The thymus gland plays an important role in the pathogenesis of myasthenia gravis and thymectomy is indicated in certain subgroups. Lambert-Eaton myasthenic syndrome is associated with antibodies directed to the voltage-gated calcium channel antibodies at the pre-synaptic nerve terminal. It is an acquired condition and, in some cases, may be paraneoplastic, often secondary to underlying small cell lung carcinoma. Clinical presentation is distinct from myasthenia gravis, with patients often first presenting with lower limb muscle fatigability and autonomic symptoms. Congenital myasthenic syndromes are inherited neuromuscular disorders due to mutations in proteins at the neuromuscular junction. Various phenotypes exist depending on the protein mutation. Treatment is directed towards symptom control and immunosuppression is not indicated.

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INTRODUCTION

The neuromuscular junction (NMJ) is a sophisticated apparatus that allows rapid and efficient transmission of impulses from nerve to muscle, resulting in muscle contraction. Because the NMJ lacks a blood–nerve barrier, it is vulnerable to autoimmune attack. Antibodies directed to the nicotinic acetylcholine receptor (AChR) on the post-synaptic muscle membrane result in the most common acquired immune-mediated NMJ disorder, myasthenia gravis (MG; see Figure 1). Antibodies directed to the voltage-gated calcium channels (VGCCs) at the pre-synaptic nerve terminal result in the less common Lambert-Eaton myasthenic syndrome (LEMS). Antibodies to the voltage-gated potassium channel antibodies, also at the pre-synaptic nerve terminal, result in neuromyotonia (Isaac's syndrome). Genetic mutations of proteins that constitute the NMJ result in congenital myasthenic syndromes.

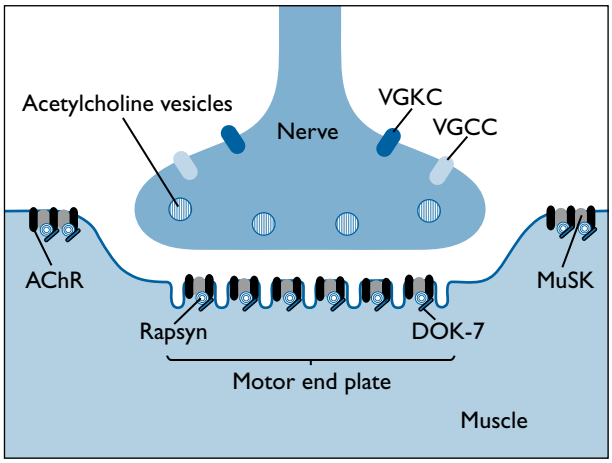

FIGURE 1 Cartoon of the neuromuscular junction and important proteins involved in the main neuromuscular junction defects. (AChR=acetylcholine receptor; MuSK=muscle-specific tyrosine kinase; VGCC=voltage-gated calcium channel; VGKC=voltage-gated potassium channel.)

MYASTHENIA GRAVIS

Myasthenia gravis affects 100 patients per million population. The incidence is bimodal, with early-onset MG typically affecting young women (<40 years) and late-onset MG affecting older men (>60 years). As a result of improved diagnosis and survival, the prevalence of MG is increasing, particularly in the elderly population.

Myasthenia gravis is characterised by fatigable muscle weakness, which can affect any skeletal muscle. Commonly, MG affects the ocular muscles first. This results in ptosis and diplopia. In about 15% of cases, MG remains purely ocular but in the majority evolves into 'generalised MG'. Proximal limb muscles are frequently affected, arms usually first. Weakness of the lower facial muscles results in a characteristic myasthenic snarl (rather than a smile) and in dysarthric speech. Bulbar muscles (those muscles responsible for swallowing, chewing, articulation and vocalisation) may be affected. Axial muscle weakness (especially neck flexion weakness) may occur. Neck extension weakness results in 'head drop'. This renders the patient more susceptible to aspiration but is not

TABLE 1 Differential diagnosis of head drop

Neuromuscular
Myasthenia gravis
Motor neurone disease
Inflammatory myopathies (e.g. polymyositis)
Other muscle conditions, e.g. myotonic dystrophy type 1, mitochondrial cytopathies, facioscapulohumeral muscular dystrophy
Central
Parkinsonism
Multiple systems atrophy
Spasmodic torticollis
Iatrogenic
Botulinum toxin treatment
Rare but described
Hypothyroidism
Hyperparathyroidism

Modified from: Beekman R, Tijssen CC, Visser LH et al. Dropped head as the presenting symptom of primary hyperparathyroidism. *J Neurol* 2002; 249:1738–9. doi:10.1007/s00415-002-0898-7

specific for MG (see Table 1). When severe, MG can affect respiratory muscles, including diaphragmatic muscles, and the patient may require respiratory support either in an intensive care setting or non-invasive ventilation (for example, bilevel positive airway pressure). An MG crisis implies a deterioration of bulbar and/or respiratory muscles such that the patient requires feeding via a nasogastric tube, often with intubation and mechanical ventilation requiring management in an intensive care unit.

Pathogenesis

What causes MG is unknown. Presumed culprits include a genetic predisposition to autoimmunity (including gender) and some infections. Early-onset AChR antibody-positive MG is associated with particular human leucocyte antigens (HLA), including DRB1*03, DQA1*0501, DQB1*0201. The thymus gland is important in MG immunogenesis as it has the full immunological repertoire to mount an immune response to the nicotinic AChR. The thymus gland in AChR-antibody-positive MG is hyperplastic in about 85% of cases and harbours thymoma in a further 10%. The remaining MG patients, especially those with late-onset MG, have thymic atrophy.

Antibodies in myasthenia

Patients with purely ocular MG have detectable AChR antibodies in about 50% of cases. In contrast, AChR antibodies are present in about 80% of patients with generalised MG. The remaining patients are referred to as 'seronegative'. In this subgroup, around 50% have antibodies to muscle-specific tyrosine kinase (MuSK). MuSK is a protein located at the post-synaptic membrane, which is responsible for clustering of the AChR at the muscle membrane surface. MuSK-MG can be

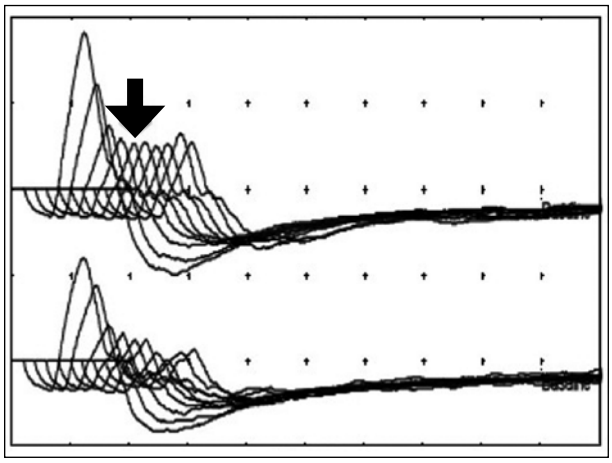

FIGURE 2 Repetitive nerve stimulation studies to nasalis in a patient with myasthenia gravis, showing significant decrement between the first and fifth compound muscle action potentials (arrow). (With kind permission of Dr Arup Mallik, Consultant Neurophysiologist, Glasgow.)

indistinguishable from AChR-MG, but, in some cases, patients can present with predominantly bulbar muscle weakness and some patients may be refractory to conventional treatments. Of the remaining generalised MG patients without detectable antibodies, a proportion harbour low-affinity AChR antibodies. These can be detected in a newly described cell-based assay, which is not yet commercially available.

Investigations for myasthenia

If MG is suspected, the patient's serum should be tested for AChR antibodies. If these are negative, then MuSK antibodies should also be tested, even if only ocular symptoms are present.

Neurophysiological testing should be performed to confirm the diagnosis of MG, especially if antibodies are undetectable or testing not available. In MG, repetitive nerve stimulation (RNS) studies show a significant decremental response (>9%) between the first compound muscle action potential (CMAP) and the fourth or fifth CMAP when the nerve to an affected muscle is stimulated (Figure 2). Nerves commonly tested include the ulnar, radial, accessory and/or facial nerves. While specific for MG, there are a number of technical issues with RNS which can result in false positives and false negatives.

Single-fibre electromyography (SFEMG) is a more sensitive test, in which adjacent single muscle fibres are analysed to determine how time-locked their responses are with respect to each other. With significant neuromuscular junction instability, the time taken for the nerve action potential to cross the NMJ becomes variable, generating increased 'jitter' (Figure 3). With profound weakness, impulse blocking can be detected. Single-fibre electromyography can also be abnormal in other conditions (e.g. radiculopathy, motor neurone disease or mitochondrial myopathy).

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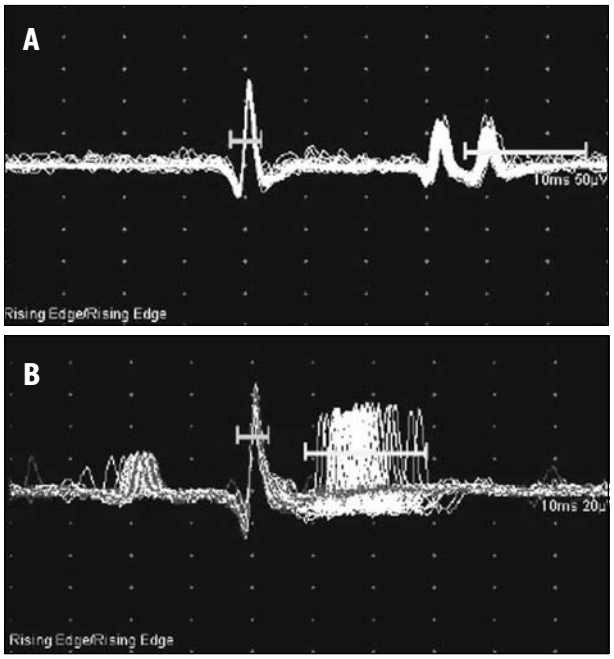

FIGURE 3 Single-fibre EMG studies. A: Superimposed single muscle potentials show minimal jitter in a normal study. B: Varying and increased jitter is seen, reflecting neuromuscular junction instability in a patient with myasthenia gravis. (With kind permission of Dr Arup Mallik, Consultant Neurophysiologist, Glasgow.)

The Tensilon test is a bedside test in which edrophonium, a short-acting acetylcholinesterase inhibitor, is administered intravenously. The aim of the test is to demonstrate reversibility of muscle weakness. The test should only be performed if unequivocal weakness can be demonstrated (for example, ptosis) and it should be performed double-blind and placebo-controlled. There is a risk, especially in the elderly, of inducing significant bradycardia and cardiac arrest on administering intravenous edrophonium, so a cardiac arrest trolley should be kept close at hand. For this reason, many physicians administer atropine prophylactically.

Imaging of the thorax (computed tomography or magnetic resonance imaging) should be performed in all MG patients, irrespective of antibody status, to exclude the presence of an anterior mediastinal mass, which could represent thymic hyperplasia or thymoma.

Treatment

For mild MG, symptomatic treatment with pyridostigmine, an acetylcholinesterase inhibitor, is often sufficient. Pyridostigmine makes more acetylcholine available to the intact AChRs and thereby improves muscle strength. Its therapeutic potential is limited and the half-life means that it wears off after 5–6 hours. For patients who do not respond adequately to pyridostigmine, immunosuppression is important to induce remission. This usually involves a combination of corticosteroids and a steroid-sparing agent (commonly azathioprine). Corticosteroids prescribed at high dosage may initially exacerbate MG and lead to crisis so most physicians start at low doses and build up the dose gradually until symptoms resolve. If azathioprine is not tolerated or if the MG proves refractory, alternative immunosuppressive agents such as mycophenolate mofetil, ciclosporin or methotrexate can be tried. Rarely, drugs such as cyclophosphamide and rituximab, a monoclonal antibody to CD20, have been used to treat refractory MG patients.

Myasthenia gravis crisis should be treated in an intensive care unit, especially when mechanical ventilation is required. Myasthenia gravis status is improved rapidly using plasmapheresis (usually five exchanges) or intravenous immunoglobulin (a five-day course prescribed at 0.4 g/kg/day). In some refractory cases, in which immunosuppression is inadequate, remission can be achieved and maintained by repeated treatment with immunoglobulin or plasmapheresis.

Thymectomy is indicated in all patients with evidence of anterior mediastinal mass on thoracic imaging and also in patients with AChR antibody-positive generalised MG who are 50 years or younger and whose symptoms have been ongoing for two years or less. This is not evidence-based, however, and it is still uncertain whether the duration of MG symptoms should influence the decision for thymectomy. The ongoing international thymectomy trial should help us further with deciding who are the right candidates for thymectomy. It is not clear whether patients with thymic atrophy also benefit from thymectomy and the trial may help us to answer this, too. In patients with malignant thymoma, additional therapy in the form of radiotherapy or chemotherapy may be indicated.

Myasthenia gravis triggers

Physical or emotional stress can trigger or exacerbate MG, as can significant infections. Surgery could be considered as an example of physical stress to the body. If the patient is already established on treatment, then a small increase in dosage of pyridostigmine and/or steroids may be indicated, but this should be tailored according to the individual patient and their circumstances.

The first trimester of pregnancy may also cause a flare-up of MG symptoms, but MG status tends to improve during the second and third trimester. Fatigue becomes prominent as the pregnancy advances.

Many classes of drugs are known to exacerbate MG and should be avoided or used with caution. Some examples have been listed in Table 2. It is important to note that the use of telithromycin, a macrolide, is absolutely contraindicated in MG. Live vaccines should be avoided in MG patients receiving immunosuppression. Thyroid disease, which can coexist with MG, can exacerbate or unmask MG weakness when untreated, while over-replacement with levothyroxine may also

TABLE 2 List of drugs to avoid or use cautiously in myasthenia gravis

Antibiotics
Aminoglycosides, e.g. gentamicin, neomycin – AVOID
Antimalarials, e.g. chloroquine, mefloquine, quinine – AVOID
Macrolides, e.g. clarithromycin, erythromycin – CAUTION
Telithromycin – ABSOLUTELY CONTRAINDICATED
Cardiovascular
Anti-arrhythmics, e.g. procainamide – AVOID
Beta blockers, e.g. atenolol – CAUTION
Calcium channel blockers – CAUTION
Statins – CAUTION
Diuretics – CAUTION
Rheumatological
Pencillamine, hydroxychloroquine, colchicine – AVOID
Analgesia
Strong opiates – AVOID
Benzodiazepines – AVOID
Gastrointestinal and urinary
Anticholinergics, e.g. hyoscine, oxybutynin – CAUTION
Propantheline (anticholinergic) – used safely in MG, often to counteract pyridostigmine side effects
Magnesium in antacids and laxatives – AVOID
Topical eye preparations
Bacitracin, polymyxin, beta blockers – AVOID

Summarised from Murray L, Carmichael C, Farrugia ME. *Medicines that may affect patients with myasthenia gravis*, 2010. Available from: Neurology Department, NHS Greater Glasgow & Clyde.

cause MG exacerbation. If an MG patient requires general anaesthesia, the anaesthetist ought to be aware of this diagnosis. Neuromuscular blocking agents should be used cautiously since MG patients are particularly sensitive to non-depolarising agents and the response to depolarising drugs is variable.

Prognosis

Ocular MG is relatively benign but still disabling if ophthalmoparesis is refractory to treatment. Childhood-onset MG bears a good prognosis, with the majority going into spontaneous remission. Myasthenia gravis associated with thymoma can be more difficult to treat and patients are more vulnerable to relapse. Because most patients are commenced on immunosuppression at disease presentation, it is difficult to ascertain the rate of spontaneous remission in the adult population, but this is thought to stand around 10%. The majority of patients will achieve significant stabilisation of MG status with minimal manifestations and only a minority will be refractory to treatment. Predominant bulbar presentations obviously carry higher morbidity and mortality risks especially in the elderly. The overall mortality rate in MG is 3–5%.

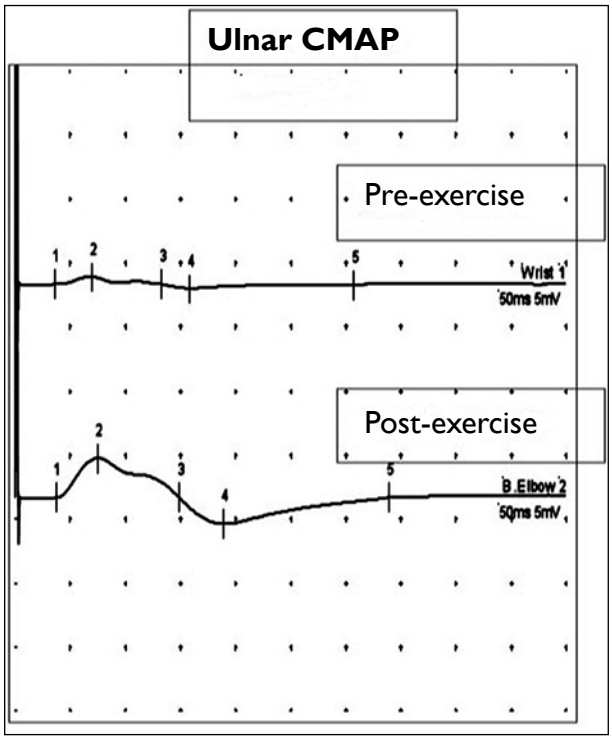

FIGURE 4 Nerve conduction studies on the ulnar nerve in a patient with Lambert-Eaton myasthenic syndrome. The baseline compound muscle action potential (CMAP) is very small, but facilitation follows exercise with significant increment in the size of the CMAP. (With kind permission of Dr Arup Mallik, Consultant Neurophysiologist, Glasgow.)

LAMBERT-EATON MYASTHENIC SYNDROME

Lambert-Eaton myasthenic syndrome (LEMS) is an acquired immune-mediated condition, associated in 90% of cases with antibodies to the voltage-gated calcium channels (VGCCs) on the pre-synaptic nerve terminal. The VGCC is crucial in allowing calcium entry into the nerve terminal and thereby facilitating the release of acetylcholine vesicles.

The clinical presentation of LEMS is different from that of MG. Lower limb muscle weakness is more prominent as an initial symptom, and weakness affecting upper limbs, face, and ocular muscles occurs later. Autonomic features, such as dry mouth, dry eyes and sphincter dysfunction, may be present. The typical waddling gait of patients with LEMS is due to a combination of proximal lower limb weakness and the fact that VGCC antibodies also attack receptors on cerebellar granule cells, resulting in central ataxia. The reflexes in LEMS patients are significantly reduced or absent but will often return after exercise. This is known as potentiation of the reflex. Lambert-Eaton myasthenic syndrome can be seen as a paraneoplastic syndrome, often associated with small cell lung cancer.

A search for underlying malignancy should take place in all patients presenting with LEMS and continue for the

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first five years after symptom onset, with a particularly high index of suspicion in male smokers. Neurophysiological findings in LEMS include small amplitude CMAPs at rest, which increase in size after brief exercise (Figure 4).

Symptomatic treatment in LEMS consists of 3,4-diaminopyridine (3,4-DAP), which blocks voltage-gated potassium channels, prolonging the nerve action potential and thus enhancing calcium entry. Pyridostigmine may also help. The immunosuppression strategy is essentially the same as in MG, but with caution in paraneoplastic LEMS, and intravenous immunoglobulin or plasmapheresis may also be useful.

CONGENITAL MYASTHENIC SYNDROMES

Congenital myasthenic syndromes are extremely rare (about five cases per million in the UK) inherited forms of myasthenic syndromes. Most, but not all, present with muscle weakness from birth. They are often a result of mutations affecting one of the AChR subunits (commonly the epsilon subunit), but mutations affecting other proteins at the post-synaptic membrane such as rapsyn (a cytoplasmic membrane-associated protein associated with the intracellular portion of AChRs and crucial in the AChR clustering process) and DOK-7 (downstream of kinase, important in formation of AChR clusters and of the neuromuscular synapse) are almost as common (Figure 1).

Treatment with immunosuppression is not indicated in these cases. The phenotype varies depending on the specific mutation. Most but not all patients with congenital myasthenic syndrome benefit from treatment with 3,4-DAP or pyridostigmine. Ephedrine and/or salbutamol are also effective in syndromes associated with DOK-7 mutations. Patients with slow channel syndromes (the only autosomal dominantly inherited congenital myasthenic syndrome in which AChR channel opening is prolonged) usually respond to fluoxetine or quinidine.

KEY POINTS

- Myasthenia gravis is an acquired, immune-mediated disorder of the neuromuscular junction, characterised by fatigable muscle weakness and often associated with the presence of antibodies to the post-synaptic nicotinic acetylcholine receptor. It is treatable in the vast majority of cases.
- The clinical history and examination should suggest myasthenia gravis. The diagnosis should be confirmed with antibody testing and/or neurophysiological investigation.
- Treatment is initially symptomatic with pyridostigmine, but generally requires immunosuppression with corticosteroids and other agents such as azathioprine. Thymectomy, intravenous immunoglobulin or plasmapheresis may also be appropriate.
- Myasthenia gravis is potentially life-threatening, especially if the diagnosis is missed and the condition left untreated.
- Lambert-Eaton myasthenic syndrome is an acquired pre-synaptic neuromuscular junction disorder, associated in most cases with voltage-gated calcium channel antibodies. It can be paraneoplastic. The pattern of muscle weakness is distinct from that of myasthenia gravis, with a caudal–cranial distribution.
- Inherited conditions of the neuromuscular junction (congenital myasthenic syndromes) are extremely rare. The history of fatigability usually dates back to childhood, and sometimes to neonatal or infancy periods.

FURTHER READING

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USEFUL WEBSITES

- **Myasthenia Gravis Association (UK)**: www.mga-charity.org
- **Myasthenia Gravis Foundation of America**: www.myasthenia.org
- **Euromyasthenia:** www.euromyasthenia.org

EDUCATION

SELF-ASSESSMENT QUESTIONS

1. The diagnosis of myasthenia gravis (MG) is most accurately determined by which one of the following?

A. The symptoms described by the patient.
B. The antibody result.
C. The single-fibre electromyography (SFEMG) findings.
D. If computed tomography (CT) scan of the thorax reveals a thymic mass.
E. A combination of history provided by patient, supported by clinical examination and elicitation of muscle fatigability and by the presence of relevant antibodies and/or abnormal neurophysiological findings.

2. Which one of the following statements is most correct?

A. AChR antibodies are commonly present in generalised MG.
B. AChR antibodies are always present in ocular MG.
C. Patients with MuSK antibodies will also have AChR antibodies.
D. If antibodies to AChR and to MuSK are negative but neurophysiology shows a decremental response, then the patient is unlikely to have MG.
E. AChR antibodies always indicate the presence of thymoma or other thymic abnormality or lung cancer.

3. Which one of the following patients is most suitable for consideration for thymectomy?

A. A 28-year-old patient presenting with mild ocular symptoms in keeping with ocular MG and with positive AChR antibodies.
B. A male patient aged 80 years with generalised MG, positive AChR antibodies and a normal CT scan of the mediastinum.
C. A female patient aged 25 years with generalised MG and MuSK antibodies.
D. A patient aged 40 years with generalised MG, positive AChR antibodies and a thymic mass.
E. A female patient aged 35 years with generalised MG, positive AChR antibodies and a normal CT scan of the chest.

4. Which one of the following statements is the most correct?

A. All MG patients should be treated with high doses of pyridostigmine alone and if they do not respond they should be commenced on high doses of corticosteroids.
B. MG patients with significant weakness will require symptom control with pyridostigmine and the initiation of immunosuppression with corticosteroids and a steroid-sparing agent.
C. All MG patients should be immunosuppressed irrespective of antibody status, age or disease severity.
D. When MG patients first present, they must all receive intravenous immunoglobulin or plasma exchange to improve symptoms quickly.
E. When an MG patient presents within two years of symptom onset, the treatment of choice is always thymectomy.

5. A mother attends the clinic with her 15-year-old daughter who has fatigable droopy eyelids and mild weakness around her shoulders. Her motor developmental milestones were normal, but she was always thought to run slower than her peers at school. What is the most suitable next step?

A. Test her acetylcholine receptor antibodies and start her on pyridostigmine and immunosuppression because she is likely to have MG.
B. Refer her for thymectomy, since she is likely to have immune-mediated MG associated with thymic hyperplasia.
C. Test her acetylcholine receptor antibodies, and in the clinic ask for details about her neonatal and infancy phases, family history and parental consanguinity.
D. Consider investigation with repetitive nerve stimulation studies and SFEMG studies.
E. Give her a course of plasma exchange to determine between immune-mediated and congenital myasthenic syndrome.

This paper was originally published as part of the Neurology module in the RCPE Online Continuing Medical Education Programme. Online CME, including the anwers to these questions, is available to Fellows and Members at: http://www.rcpe.ac.uk

EDUCATION

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